REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 40-90 are in this case.

Claims 40-90 were rejected under 35 U.S.C. 103(a) as being unpatentable over Heese et al. (U.S. Patent No. 6,623,759) in view of Bergstrand et al. (U.S. Patent No 5,817,338).

Applicant respectfully traverses these rejections. Claims 40, 48, 65, 83 and 90 have now been amended. New claim 91 has been added.

35 U.S.C. § 103(a) rejections

The Examiner has rejected claims 40-90 under 35 U.S.C. 103(a) as being unpatentable over Heese et al. (U.S. Patent No. 6,623,759) in view of Bergstrand et al. (U.S. Patent No 5,817,338). The rejections of the Examiner are respectfully traversed.

The present invention provides a formulation for a benzimidazole, such as omeprazole, which is able to maintain the stability of the active ingredient during both storage and during passage through the stomach, and which does not require a separating layer between the core and the enteric coating layer. The taught formulation uses an enteric coating having a pH of at least 6.5, in order to prevent the known reaction between the alkaline core and the acidic enteric coating occurring in prior art formulations which are devoid of an intermediate layer.

Heese et al. neither teach nor suggest either a formulation devoid of an intermediate layer between the core and the enteric coating, or an enteric coating having a pH of at least 6.5. As stated in column 3, lines 49-60, Heese et al. teach a stable medicament comprising a core comprising omeprazole, lansoprazole or pantoprazole, an intermediate layer applied to the core, and a gastric juice-resistant outer layer, characterized in that a reactive intermediate layer of gastric juice-resistant polymer layer material partially neutralized with alkali with cation exchange capacity is present in the intermediate layer.

Applicant agrees with the Examiner's observations that various materials may be used for the enteric coating, including cellulose acetate phthalate and polymethacrylates (column 6, lines 5-20); and that the enteric coating may contain a plasticizer such as triethyl citrate (column 7, lines 5-9).

However, the Examiner has further stated, (referring to column 6, lines 62-67) that the enteric coating is preferably applied as an aqueous dispersion and neutralized to a pH value of around 5.5 to around 7.0. The aqueous dispersion referred to in Bergstrand is, in fact, an intermediate layer, as disclosed on column 6, line 62-column 7, line 2, which teaches that the molded articles are 'laminated with an aqueous dispersion....in a fluidized bed apparatus, for example, under formation of the intermediate layer with cation exchange activity'. Furthermore, column 7, lines 5-9, teach that the product is subsequently coated with a gastric juice-resistant substance for formation of the enteric outer layer of the medicament according to the invention. The use of suitable bases, as referred to by the Examiner (column 5, lines 12-20) are for neutralization of the intermediate layer, and not of the enteric coating layer (see column 5, lines 1-6).

The Examiner has further stated that claims 58-60 and 76-78 contain limitations reciting a percentage value of the degree of neutralization of an enteric coating material, and considers that such properties are inherent in an enteric coating material of the prior art when the pH of an enteric coating is adjusted to a particular value using known methods. The Examiner has further stated that the degree of neutralization as it correlates to the pH of an enteric coating material has already been contemplated by the prior art (column 5, lines 1-12), such that these claims are considered to be obvious in view of the prior art.

Applicant respectfully disagrees with the Examiner's assertions. Heese et al. (column 5, lines 1-12) teach neutralization of an intermediate layer, and not of an enteric coating devoid of an intermediate layer. In contrast, the present application discloses neutralization of an enteric coating layer, which is devoid of an intermediate layer, by adjusting to a pH of at least 6.5, which can then be layered directly over the substrate (page 10, lines 17-23 of the instant application).

Although Heese et al. discuss the pH of the intermediate layer, the issue of the pH of the enteric coating and its effect on the requirement for an intermediate layer is not referred to. As stated in column 6, lines 8-9, the outer layer according to Heese et al. represents a customary enteric, gastric juice-resistant layer. As is known in the art, ordinary enteric coatings are made of acidic compounds (see, for example, GB 2189698, page 1, lines 30-31). Enteric polymeric materials are primarily weak acids containing acidic functional groups, which are capable of ionization at elevated pH. In

the low pH of the stomach, the enteric polymers are unionized, and therefore, insoluble. As the pH increases in the intestinal tract, these functional groups ionize, and the polymer becomes soluble in the intestinal fluids. Thus, an enteric polymeric film coating allows the coated solid to pass intact through the stomach to the small intestine, where the drug is then released for absorption through the intestinal mucosa into the human body where it can exert its pharmacologic effects.

The problems caused by acidic enteric coatings, and the fact that untreated enteric coatings suitable for use with benzimidazoles are by their nature acidic, are described in great detail in the prior art. For example, US 4,786,505 to Astra clearly describes the stability problems caused to omeprazole, an acid labile benzimidazole, due to the acidic properties of the enteric coating: " Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and lose in omeprazole content with the passage of time.

In order to enhance the storage stability, the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water of gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.... The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of omeprazole during the coating process or during storage. The subcoating layer, in the following defined as the separating layer, also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles ".

As stated on page 2, lines 19-21 of the present application, and as supported by the above prior art reference, in prior art formulations using an enteric coating, the alkaline core containing omeprazole was found to react with the enteric coating. Therefore, many prior art formulations have been developed which provide a subcoating layer between the acidic enteric coating and the alkaline core, in order to prevent this reaction.

Hence, the composition taught by Heese et al. comprises a conventional, acidic, enteric coating, which does not have a pH of at least 6.5, and which requires the use of an intermediate layer in order to provide stability.

While continuing to traverse the rejections of the Examiner, Applicant has chosen to amend claims 1, 48, 65, 83 and 90 to clarify that the composition is provided without an intermediate layer between the substrate and the enteric coating, in order to expedite the prosecution. Support for this amendment is derived from the specification at page 8, lines 6-8. Claim 65 has further been amended to replace the term 'consisting essentially of' with the term 'comprising'. Support for this amendment is derived from the specification at page 6, lines 16-19.

Bergstrand et al. teach a multiple unit tableted dosage form of omeprazole, the purpose of which is to provide a dosage form in which the enteric layer(s) covering the individual units of active substance has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coated layered units (column 3, lines 32-41).

As stated by the Examiner, the each individual unit according to Bergstrand et al, comprises a drug core and an enteric coating. As further stated by the Examiner, the drug core may be formed from inert cores, with the active ingredient layered over them, and the active substance may be mixed with other substances before being layered over the inert core, such as binders. However, the prior art pellets are then compressed (column 7, lines 53-55). The structure of this dosage form is therefore significantly different from that of loose pellets or tablet formulations, as taught in the instant application. Thus, teachings applied to the multiple unit dosage form of Bergstrand et al. are not necessarily applicable to other formulations.

The Examiner further states that although intermediate layers between the core and the enteric coating layer may be used, the prior art does contemplate

embodiments where the enteric coating layer is applied directly over the drug core (column 5, lines 60-67; Example 8).

Column 5, lines 60-67 states that before applying enteric coating layer(s) onto the core material in the form of individual pellets, such pellets may optionally be covered with one or more separating layer. As stated in column 6, lines 39-43, although the separating layer is not essential for the invention, it may improve the chemical stability of the active substance. Hence, it is clear that a stable composition for a benzimidazole derivative according to the teaching of Bergstrand et al. would preferably require the use of such a separating layer.

The enteric coating of Example 8 to Bergstrand et al. comprises methacrylic acid copolymer, triethyl citrate and talc. This is a conventional enteric coating, which, as discussed above, would not be expected to have a pH of at least 6.5, and therefore does not teach the present invention. The issue of the effect of pH on the requirement for an intermediate layer is not referred to in the prior art document. It is therefore clear that the use of a coating having pH of at least about 6.5 in order to provide a composition which does not comprise an intermediate layer is not taught by Bergstrand et al.

The combined disclosures of Heese et al. and Bergstrand et al. do not teach a stable benzimidazole formulation which does not require a subcoating layer, involving use of an enteric coating having a pH of at least 6.5.

In order to further expedite proceedings, claim 65 has been amended to clarify that the enteric coating material is adjusted to a pH value of at least about 6.5 by an alkaline compound, as taught in the specification at page 7, lines 8-10. Claim 83 has been amended to clarify that the present invention teaches a method for the preparation of a stable composition of a benzimidazole derivative, as taught in the specification at page 10, lines 12-15.

New claim

New claim 91 has been added, which recites a stable composition for a benzimidazole derivative, comprising a substrate featuring the benzimidazole derivative; and a neutralized enteric coating material layered directly over the substrate, having a pH value of at least about 6.5, such that there is no additional layer between

said substrate and said enteric coating. Support for this claim is provided throughout the specification, for example at page 10, lines 16-23.

The present response is intended to be fully responsive to all points of objection raised by the Examiner and is believed to place claims 40-90, as well as new claim 91, in condition for allowance. Favorable reconsideration and allowance of the Application is respectfully requested.

Respectfully submitted,

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